UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,001	07/19/2004	Nisar P Malek	14538A-006610US	6809

7590 03/06/2007

Brian W Poor
Townsend and Townsend and Crew
Two Embarcadero center
8th Floor
San francisco, CA 94111

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,001	MALEK ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/21/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *10-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 12/21/2006 has been received. Claim 8 has been amended. Claims 10-37 are withdrawn as being drawn to a non-elected invention. Claims 1-37 are pending and claims 1-9 are under consideration in the instant office action.

Applicant's traversal of the restriction requirement of 04/11/2006 is noted. However, the restriction requirement was made FINAL in the office action dated 06/21/2006. If Applicant wishes to continue to traverse the restriction requirement they may do so via petition to the Director (see 37 CFR 1.477 and 37 CFR 1.144). The basis of the requirement is reiterated below.

The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. See 37 C.F.R 1.475 (a). If multiple products, processes of manufacture, or uses are claimed, the first invention of the category first mentioned in the claims of the application and first recited invention of each of the other categories related thereto will be considered as the main invention in the claims. See 37 C.F.R 1.475 (d) and 37 C.F.R 1.476 (c). In the instant case, a special technical feature does not link the inventions of Groups I and II as they relate to materially different products or methods of making said products. The special technical feature of the elected Group II is replacement of the endogenous p27 gene with a mutant $p27^{kip1}$ gene at the location of the endogenous p27 gene. This special technical feature is not common to any of the other specified groups.

Art is not necessary to demonstrate a lack of unity if multiple products are claimed, for example. However, the Malek (2001) reference is noted. Applicant is also referred to Sheaff (1997, IDS) for teaching the claimed $p27^{Kip1}$ mutation (T187A).

This application contains claim 1, which encompasses an invention nonelected with traverse in the election dated 05/15/2006. A complete reply to the final rejection must include removal of nonelected subject matter from the claims or other appropriate action (37 CFR 1.144).

Applicant is again reminded that claim 1 is being examined as it reads on the elected invention wherein the mutant p27 gene is located at the endogenous p27 locus, resulting in a loss of endogenous, wildtype p27. If claim 1 is amended to read on the elected invention, claims 4 and 5 will be of the same scope as claim 1.

Specification

The objection to the disclosure is withdrawn because the originally filed first paragraph of the specification has been moved such that the priority information is now at the first line of the specification.

Claim Objections

Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) an isolated transgenic somatic cell or ES cell or 2) an isolated transgenic mouse primordial germ cell, oocyte, egg, spermatocyte, sperm cell, fertilized egg, zygote, each having a mutant p27 gene lacking a Cdk2 phosphorylation site located at the endogenous $p27^{Kip1}$ locus, wherein the mutant p27 gene encodes a mutant $p27^{Kip1}$ polypeptide having a longer half-life in S phase that wildtype $p27^{Kip1}$ polypeptide, does not reasonably provide enablement for a non-mouse primordial germ cell, oocyte, egg, spermatocyte, sperm cell, fertilized egg, or zygote as claimed The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is withdrawn as it relates to claim 9.

The rejection is maintained, in part, for reasons of record set forth at pages 3-6 of the office action dated 06/21/2006. Applicant has argued that homozygous somatic cells can be made in vitro using multiple rounds of gene targeting and screening (Applicant's Remarks at page 21). This argument is persuasive as it relates to both somatic and ES cells. However, as set forth in the rejection at pages 3-6 of the office action dated 06/21/2006, the germ cells or germ

cell precursors and derivatives require germline, gene-targeted animal, for which only mice were enabled by the specification and art at the time of filing.

The rejection is based on the grounds that the specification fails to enable obtaining the claimed germ cell precursors and or derivatives, requiring homologous recombination to target the endogenous p27 gene, for the breadth of animal species encompassed by the claims. More specifically, the specification does not enable recovering a homologous recombinant in a germline cell in any manner other than isolating the cell from an animal and does not enable homologous recombination, in vitro, in nondividing cells such as oocytes. The general basis of the rejection is that only mouse gene-targeted animals had been obtained routinely in the art at the time of filing. This is because only mouse ES cells are totipotent and capable of passing a gene-targeting event through the germline such that two heterozygotes can be mated to produce a homozygote. While non-mouse, heterozygous chimeras can be made in non-mouse species, the gene targeting event is not passed through the germline and eggs, oocytes, sperm cells, zygotes etc carrying the targeting even cannot be obtained. Applicant has prophetically taught use of nuclear transfer as a means to obtain transgenic, gene-targeted animals of non-mouse species. However, this procedure is highly underdeveloped and had not met success at the time of filing. Thus, the specification at the time of filing was enabling for obtaining gene-targeting events in somatic cells in vitro and gene targeting in mouse germline cells.

Applicant has advanced the following arguments in support of the routine and predictable nature of making a live animal by gene-targeting and somatic cell nuclear transfer. In carrying

out such a procedure, it would be Applicant's position that non-mouse animals obtained through this means would be a source for the germline cells encompassed by the claims.

Applicant argues that the specification describes the use of somatic cell nuclear transfer at page 21, line 209-page 28, line 18 (see page 16, paragraph 2 of Remarks)..

In response, these teachings in the specification are merely prophetic and fail to overcome the art-recognized unpredictabilities and the underdeveloped nature of gene-targeting in somatic cells followed by nuclear transfer.

Applicant continues in arguing that the art set forth in the rejection at pages 3-6 of the office action dated 06/21/2006 merely established an inefficiency of gene-targeting followed by nuclear transfer and that it does not require undue experimentation to obtain success through routine repetition as homologous recombination was known to occur at predictable frequencies (page 16, last paragraph-page 17, paragraph 2)..

In response, while a gene-targeted event may be obtained in somatic cells, in vitro, without an undue amount of experimentation, use of those cells in effecting cloning by nuclear transfer was far from routine in the art at the time of filing. There were additional complications and unpredictabilities in following through with nuclear transfer after homologous recombination in vitro, including what cell types in which species this would be effective (for example, see Williams *et al.*, **Molec. Reprod. Dev.**, 66:115-125, 2003) Mir outlines the difficulties and unpredictabilites still recognized in 2004 [**Nucl Acid Res**, 32:e25, 2004]. Harrison *et al.* taught the generation of gene-targeted porcine fetal fibroblasts but failed to yet generate pigs from the

cells using nuclear transfer [**Transg. Res.**, 11:143-150, 2002]. The specification fails to address any of these issues and does not provide any examples or guidance with how to deal with the underdeveloped nature of the art. For example, Denning taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence [**Cloning and Stem Cells**, 3:221-231, 2001, specifically refer to page 222, col. 1, lines 5-8]. In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Clearly, the art supports the unpredictability and underdeveloped nature of gene targeting using any somatic cell type for use in nuclear transfer methodologies, and more specifically, that candidate somatic cells that would be used for gene targeting must be able to survive multiple rounds of cell division, selection and overcome senescence. The specification fails to provide any specific guidance in carrying out nuclear transfer to arrive at the claimed invention in a manner to overcome the unpredictable and underdeveloped nature of the art.

Applicant argues specifically the teaching of Thomson (2003) for the assertion that somatic cell nuclear transfer was highly underdeveloped (page 17, last paragraph-page 20,

paragraph 1). Applicant asserts that Thomson suggests developing modifications to overcome premature senescence of primary cells in culture and that such premature senescence is primarily an issue of efficiency. Applicant points out that Thomson states that gene targeting in livestock has become a reality (page 18, paragraph 2).

In response, Applicant fails to support that the premature senescence taught by Thomson is an issue of efficiency. Primary cells in culture are incapable of undergoing enough population doublings to undergo homologous recombination and selection of proper integration events. This does not appear to be an issue of efficiency. The first gene-targeting event used in cloning by nuclear transfer occurred in 2000 using fetal fibroblast cells [McCreath, **Nature**, 405:1066-1069, 2000], and while considered "a reality" it was by no means routine and was subject to great unpredictability and significantly limited scope in terms of cell type capable of sustaining the requisite population doublings and species for which this was attainable. Thus, while at the time of filing isolated instances of gene-targeting in somatic cells followed by successful nuclear transfer had occurred, this was far from routine and its application to any gene in any cell type for any species was highly predictable as the art has established, even in light of the isolated successes. In fact, it is noted, that success in cloning in various species, regardless of transgenesis, is highly variable with respect to which cell types in different species can be reprogrammed. Certainly, at the time of filing, it was far from routine and the art was, indeed, highly underdeveloped with respect to gene targeting in somatic cells followed by nuclear transfer to obtain a live animal. The instant specification has not demonstrated gene-targeting and nuclear transfer for any cell in any species of animal.

Applicant's arguments regarding the use of non-mouse ES cells (page 20, paragraph 2 of Applicant's Remarks) is persuasive and this grounds of the rejection is withdrawn as it relates to ES cells (see page 6, paragraph 2 of the office action dated 06/21/2006).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant argues that claim 8 has been amended to more clearly set forth what is being claimed. However, the claim remains entirely unclear to the Examiner. It is not clear how the cell of claim 1 can comprise progeny of a second cell. It is not clear if Applicant is claiming a cell comprising within itself, a cell, or a cell, wherein the cell is a progeny of a cell and each of the cells has the characteristics set forth in claim 1. Applicant states that when read in light of the specification, the skilled artisan will understand the scope of claim 8. Applicant is requested to direct to Examiner to relevant aspects of the specification that will clarify the scope of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 1-7 and 9 under 35 U.S.C. 102(a) as being anticipated by Malek et al. [IDS, September 2001] is withdrawn. The Roberts Declaration under 37 CFR 1.132 filed 12/21/2006 is sufficient to overcome the rejection of claims 1-7 and 9 because Applicant has demonstrated that the applied reference under 35 USC 102(a), Malek *et al.* (2001) is Applicant's own work.

Conclusion

It is noted that Sheaff *et al* (1997) and Morimoto et al. (2000) each taught isolated cells comprising a mutant p27 lacking a Cdk2 phosphorylation site as encompassed by claim 1. However, the elected invention is drawn specifically to cells comprising a mutant p27 located at the endogenous p27 locus, eliminating wild-type p27. Thus, this art does not read on the elected invention and is not applied over the claims as examined.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio

Valarie Bertoglio
Examiner
Art Unit 1632